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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,263	11/03/2003	Huda Akil	020885-000620US	7036

20350 7590 02/13/2006

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/701,263	AKIL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *2,5 and 11-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/3/04, 6/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks filed 27 December 2005 have been entered. Claims 1 – 29 are pending.

Sequence Compliance

2. This application refers to sequences by GenBank accession number, particularly in the tables. MPEP § 2422.03 permits reference to prior art sequences by accession number, unless the examiner considers the material to be "essential". In this case, applicant's election filed 27 December 2005 explicitly named FGFR2 (GenBank accession number M80634) as the elected nucleic acid. Thus recitation of this specific nucleic acid sequence appears to be essential to the scope of the claimed invention. Consequently, applicant is required to identify this nucleic acid by SEQ ID NO: in response to this office action and to file a sequence listing consistent with the rules set forth in MPEP Chapter 2400.

Note that failure to respond to this requirement will be considered non-compliant, and may result in adandonment.

Election/Restrictions

3. Applicant's election with traverse of Group II in the reply filed on 27 December 2005 is acknowledged. The traversal is on the ground(s) that because the nine inventions "all stem from a common concept and theory" they should be examined together, and that examination of all nine groups together would not place a substantially greater burden on the examiner. This is not found persuasive because the criteria for restriction are not whether or not inventions stem from a common concept or theory, but rather whether they are independent and distinct. The restriction requirement mailed 15 September 2005 clearly set forth the reasons that each invention is distinct from one another, and applicant has not provided any evidence that the examiner's reasoning was incorrect. Furthermore, consideration of multiple inventions together is very burdensome, especially when each invention is a method that requires different steps and different starting materials.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 2, 5, and 11 – 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking

claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 27 December 2005.

5. Claims 1, 3 – 4, and 6 – 10 are under examination.

Claim Objections

6. Claims 1, 3 – 4, and 6 – 10 are objected to because of the following informalities: they encompass non-elected subject matter, as the claims encompass any and all nucleic acid sequences in tables 2 – 4 as well as proteins encoded by those sequences. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3 – 4, and 6 – 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting expression of human FGFR2 nucleic acid in anterior cingulate gyrus tissue from a post-mortem sample, wherein a decrease in the expression of the nucleic acid indicates that the patient had or was treated for major depressive disorder, does not reasonably provide enablement for concluding that the patient has or is predisposed to major depressive disorder, or that the patient has or is predisposed to any other mood disorder, or for any other tissue other than the dorsolateral prefrontal cortex, or for detection of protein as a tool for determining if a patient has a mood disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

Claim 1, from which claims 3 – 4 and 6 – 10 depend, encompasses determining whether or not a patient either has or is predisposed to a mood disorder. The base claim is very broad. The specification does not provide enablement for determining if a patient either has or is predisposed to a mood disorder. The only working example in the specification (p. 59) describes the results of experiments performed on post-mortem human tissue. Because the tissue was taken from patients who were already dead and already had been diagnosed with either major depressive disorder (MDD) or bipolar disorder (BP), it was not possible to determine if the patients will develop either disorder, as the disease states of the dead do not progress. Furthermore, it is entirely unclear whether the changes observed are the cause of or the result of the mood disorder. In fact, almost a year after this application was filed, many of the inventors published a paper specifically pointing this out (see Evans et al. 2004. Proc Natl. Acad Sci USA 101:15506-15511, particularly p. 15510, last complete paragraph). Thus the specification does not provide sufficient enablement for determining if a patient is predisposed to the mood disorder. The only way to really determine whether or not gene expression indicates that a patient is predisposed to a disorder is to first obtain the gene expression data at a time before the patient has any mood disorder, and then follow the patient noting if he or she develops said disorder, and then determine whether or not the observed gene expression is correlated with a different frequency of the disorder.

Furthermore, the specification does not provide enablement for the full scope of claim 1 and dependent claims 6 - 10. The base claim encompasses contacting the sample with a reagent that "associates with a polynucleotide or polypeptide". The working example in the specification only discloses the results of experiments in which nucleic acids were used for detection. The Affymetrix microarray consists of oligonucleotides; nucleic acids derived from patient samples are contacted with the microarray. Proteins are not used in the GeneChip experiments. Clearly the only data presented in the specification are drawn to nucleic acids, defined by both structure and function. However the claims do not recite any particular nucleic acid structure or function.

The art recognizes that while some have assumed that protein levels can easily be predicted from nucleic acid data, this is not the case. Haynes (1998. Electrophoresis 19:1862-1871) teaches that there is not a statistically reliable correlation between mRNA levels and protein expression; mRNA levels can vary up to 40-fold without a corresponding change in protein levels (see particularly p. 1863). Furthermore Chen (2002. Molecular & Cellular

Proteomics 1:304-313) further supports this general finding and shows that it holds true in a disease state (cancer) as well; for 165 proteins examined the correlation coefficient relating mRNA level to protein level varied from 0.442 to -0.467, and the average, collapsed across all observations, reveals no statistically significant correlation (see abstract). Thus on the basis of the scientific evidence the artisan would not conclude that a change in mRNA level reflects a change in protein level. Therefore, the changes observed in the nucleic acid level of FGFR2 are not sufficient to enable the method of claim 1 which encompasses measuring protein.

The claims as written do not direct the artisan to which nucleic acids or proteins should be measured. Many of the genes in tables 2 – 4 do not appear to be associated with mood disorders. Table 4 shows that only a subset of the genes listed were actually confirmed, either by RT-PCR or by anti-depressant studies, to be differentially expressed in depressed versus normal tissue. Thus it appears that many of the genes initially identified as differentially expressed are in fact false positives. Microarrays are well-known to be particularly susceptible to revealing false positives. While Affymetrix GeneChips only give 1 – 2% false positives, because thousands of genes are measured at once, one would reasonably expect to find several hundred false positives (see Mills et al. 2001. Nature Cell Biology 3:E175-E178, particularly p. E175, second column). Mills teaches that in situ hybridization and RT-PCR are useful ways to confirm gene chip data. Thus only those genes first identified in the microarray assay that have actually been validated by an independent method are deemed to be enabled for purposes of the claimed assay. The examiner notes that FGFR2 has been demonstrated to be differentially expressed in the RT-PCR assay (Table 4, first page).

Claims 1, 3 – 4, and 6 – 10 all encompass the genus "mood disorder" in a generic way; none of the dependent claims recite a specific mood disorder. Even FGFR2, which applicant explicitly elected as the single nucleic acid to which prosecution would be limited, is not differentially expressed in all mood disorders. Figure 9 clearly indicates that compared to controls, FGFR2 mRNA is down-regulated in MDD, but is not changed in BD. Thus the specification is not enabling for determining if a patient has a mood disorder in a general sense; for the purposes of FGF2R nucleic acid, it is only enabling for retrospective determination if a patient had major depression.

Additionally, the specification is not enabling for biological samples as broadly claimed in claim 1 or as specifically recited in claim 7. The only working example in the specification was performed with brain tissue. The specification broadly defines biological sample as including

blood, saliva, CSF, urine, or tissue (specification, p. 59, paragraph 225). The skilled artisan would not expect that the nucleic acid encoding FGFR2 would be found in any tissue than brain, for the purposes of diagnosing major depression. While FGFR2 is certainly expressed in other tissues, as mood disorders are disorders of the brain, whether or not a receptor for an FGF is differentially expressed in a non-neural tissue appears to be completely irrelevant to depression. Additionally, as clearly indicated in Table 3 of Evans et al. (p. 15508), FGFR2 down-regulation was not confirmed by RT-PCR in the anterior cingulate samples. Thus because the only working example in the specification indicates that the differential expression of FGFR2 is restricted to a very small brain region, the claimed method is not considered enabled for all biological samples.

Claim 6 recites the limitation "wherein the level of reagent that associates with the sample is different from a level associated with humans without a mood disorder". The recitation of this limitation in the dependent claim implies that the base claim encompasses a broader genus. Clearly the diagnostic method will only work when the level of the reagent is different between patients with the mood disorder and those who do not have it. One cannot diagnose a disorder by measuring samples which do not differ between affected an unaffected patients. Thus the full breadth of claim 1 cannot be enabled, as it appears to be claiming those non-enabled embodiments that are beyond the scope of claim 6.

Because 1) the nature of the invention, i.e. detection of minute quantities of biological material in a tissue sample, is complex, 2) the claims are broad, 3) the specification provides a single working example based on nucleic acid in specific brain regions, 4) there is not sufficient guidance in the specification to teach the artisan how to practice the method as broadly claimed, and 5) the state of the art of predicting protein levels given nucleic acids is unpredictable, it would take undue experimentation on the part of a skilled artisan to practice the method commensurate in scope with the claims.

8. Claims 1, 3 – 4, and 6 – 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 encompasses methods of determining if a whether or not a subject has a disorder, by contacting a sample with a reagent wherein the reagent associates with protein. Applicant has not described any such reagents which are effective in performing the method. Furthermore, applicant cannot be considered to have been in possession of the invention as broadly claimed, since the only data presented in the specification are the results of experiments performed with specific defined nucleic acids. As set forth in the scope of enablement rejection above, the art indicates that there are generally poor correlations between mRNA and protein expression. Thus is the absence of evidence that applicant actually was in possession of the method of determining whether a subject has or is predisposed to a mood disorder using reagents which bind to proteins, the examiner has determined that the generic method recited in claim 1 has not been described. Additionally, claim 1 recites the limitation "mood disorder". The specification describes results of experiments on brains from patients diagnosed with two specific forms of depression, and thus does not provide support for the entire genus of mood disorders, as the genus clearly encompasses much more than two forms of depression.

Claims 3 – 4 encompass nucleic acids and molecules which associate with nucleic acids, again in a generic way. The specification does not provide adequate written description for the entire genus of molecules which associate with nucleic acids, nor does it provide sufficient written description for the nucleic acids in general. There is no requirement in either claim 3 or 4 that the either the nucleic acid or polynucleotide have any particular structure or function. Thus there is not sufficient description of these terms.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3 – 4, and 6 – 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 encompasses reagents which bind to polypeptides which are encoded by nucleic acids which hybridize under "stringent conditions" to a nucleic acid sequence from the tables. This term is indefinite. The specification points out that the conditions are sequence-dependent and will be different in different circumstances (p. 17 paragraph 74). Moreover, it is

unclear whether the term refers to high- or low-stringency conditions, or perhaps to an intermediate degree of stringency

The term "selectively associates" in claim 1 is a relative term which renders the claim indefinite. The term "selectively associates" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Thus a skilled artisan could not determine the metes and bounds of claim 1.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 3 – 4, and 6 – 10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 – 4, and 6 – 10 of copending Application No. 11/158530. Although the conflicting claims are not identical, they are

not patentably distinct from each other because they appear to be identical with the exception of the numbers of the tables to which claim 1 refers in each case. The specification of the '530 application clearly encompasses detection of FGFR2 nucleic acid with a microarray (see p. 67 paragraph 294). Thus the claims in the '530 application, which are written in generic form as are the pending claims, encompass inventions which differ only in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

12. No claim is allowed.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Heiskanen et al. (2001). Analytical Cellular Pathology 22(4):229-234. The reference teaches measuring FGFR2 in biological samples, but does not teach or suggest FGFR2 expression for diagnosis of mood disorders.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
February 8, 2006

ROBERT C. HAYES, PH.D.
Primary PATENT EXAMINER